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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,754	10/20/2000	Neil Berinstein	13115	7885

7590 04/22/2009

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/693,754	BERINSTEIN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-19,21-27,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-19, 21-27, and 32-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 11/19/08 has been entered. Claims 3, 20, and 28-31 are canceled and new claims 32-33 have been added. Claims 1-2, 4-19, 21-27, and 32-33 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in the previous office action.

Claim Rejections - 35 USC 103

The rejection of claims 1-2, 4-17, 20 and 29-30 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, is withdrawn over canceled claims 20 and 29-30 and maintained over previously pending and new claims 1-2, 4-17, and 32-33. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

In regards to applicant's new claim 33, note that neither Hurpin et al. nor Hodge et al. teaches to co-administer an adjuvant along with the vector encoding the tumor antigen. In regards to new claim 32, it is noted that the cited references provide a reasonable expectation that

intranodal administration would induce immune responses greater than that produced by subcutaneous immunization. Specifically, Hurpin et al. teaches that whereas administration to lymphatic tissue, such as the spleen, generated substantial antigen specific CTL response, subcutaneous administration of vaccinia encoding p53 failed to generate antigen specific CTL (Hurpin et al., pages 210-211). Even when priming occurred using intravenous administration, boosting using a subcutaneous route of administration resulted in the failure to generate an antigen specific response (Hurpin et al., page 211). Please note that the site of subcutaneous injection used in Hurpin was not localized to the vicinity of a lymph node. Thus, based on the teachings of Hurpin et al., the skilled artisan would have expected that delivery of vaccine to lymphatic tissue, whether spleen or lymph node, would generate increased immune responses over subcutaneous delivery. Lehner et al. further provides evidence that subcutaneous administration is only effective when the subcutaneous injection is specifically localized to the immediate vicinity of a lymph node, i.e. targeted lymph node administration. Therefore, the combination of teachings of Hurpin et al. and Lehner et al. provide a reasonable expectation that intranodal administration would generate immune responses greater than those observed using subcutaneous injection.

The applicant argues that none of Hurpin et al., Hodge et al., or Lehner et al. teach direct intranodal administration of a vaccine and that Rice et al. provides insufficient support for an obviousness rejection because in their opinion Rice does not provide sufficient guidance for intranodal injection. In response, as noted in previous office actions, Rice et al. specifically teaches that administration both directly and indirectly to a lymph node is the preferred method

of immunization. Thus, Rice et al. provides clear direction to preferentially use direct intranodal administration to induce immune responses.

The applicant reiterates their argument that Lehner et al. teaches a subcutaneous technique, not direct intranodal administration, and that this technique is similar to the control subcutaneous technique disclosed by applicant as being less effective in generating immune responses than direct intranodal administration. In response, it is first noted that Hurpin et al. teaches the successful generation of anti-53 CTL responses in mice following either a single or multiple intrasplenic injections of ALVAC encoding p53. As previously noted, the spleen is a lymphatic tissue. Further, as discussed above, Hurpin et al. shows that direct administration to a lymphatic tissues generates substantially greater immune responses than subcutaneous administration. In fact, Hurpin et al., like applicant, shows that subcutaneous administration failed to generate antigen specific CTL against p53. Thus, Hurpin shows that administration to lymphatic tissue can induce antigen specific immunes greater than that induced by subcutaneous administration, which can be further be increased by subsequent administrations to lymphatic tissue.

Further, Lehner et al. was cited for demonstrating that the delivery of an antigen such that the lymph node is specifically targeted generates increased immune responses to the antigen as compared to other routes of administration. As stated in previous office actions, Lehner et al. showed that a direct comparison of intramuscular versus intradermal versus targeted iliac lymph node immunization revealed that targeted iliac lymph node administration of antigen resulted in increased T and B cell mediated antigen-specific immune responses (Lehner et al., page S489, and page S491). The targeted iliac lymph node administration technique, while subcutaneous,

administers the antigen close to both the internal and external iliac lymph nodes, ensuring direct exposure of the lymph nodes to the administered antigen. The applicant now argues that the Lehner method results in delivery of the antigen about 2-4 cm from the closest lymph node and that somehow this makes the targeted iliac lymph node immunization technique of Lehner analogous to applicant's non-targeted subcutaneous injection, citing Lehner et al. (1994) J. Immunol., Vol. 153, 1858-1868. This is not agreed. First, please note that the cited passage from the 1994 paper teaches that the internal iliac lymph node is found distal to the femoral vessels and about 2 to 4 cm s.c. This passage does not state that the targeted delivery technique of Lehner delivers the vaccine 2-4 cm from a lymph node. This passage states that the iliac lymph nodes are located 2-4 cm subq and just distal to the femoral vessels. Thus, the 1994 paper cited by applicant provides evidence that the location of the internal iliac lymph node was known at the time of filing such that a subcutaneous injection could be directed close to the internal iliac lymph node. In contrast, applicant's subcutaneous administration technique was not designed to target any particular lymph nodes, and there is no indication in the specification that the applicant's subcutaneous injections were in fact administered in close proximity to any particular lymph node or nodes in the dorsal cervical/ interscapular regions. In addition, the fact that Lehner et al. generated substantial antigen specific immune responses using their targeted iliac lymph node immunization technique whereas both Hurpin et al. and applicant's were not able to generate antigen specific immune responses greater than controls using subcutaneous administration provides clear evidence that targeted delivery of antigen in the vicinity of lymph node has a substantial effect in enhancing immune responses. Thus, applicant's subcutaneous

administration technique appears to resemble that of Hurpin et al. and does not appear to be analogous to the targeted lymph node administration technique used successfully by Lehner et al.

Further, the rejection of record is based on the knowledge available to the skilled artisan at the time of filing. Lehner et al., as discussed above and in previous office actions, clearly demonstrates successful generation of immune response by targeted administration of antigen in close proximity to lymph nodes. In addition, all of Hurpin et al., Rice et al., and Lehner et al., teach that lymphatic administration successfully generates immune responses, and Rice and Lehner et al. particularly point to targeting the lymph node either directly or indirectly with antigen to induce immune responses. Taken as a whole, the combined teachings of the cited references demonstrate that the skilled artisan at the time of filing would have had a reasonable expectation that direct intranodal administration of an antigen would induce an immune response. The applicant is also reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Thus, for reasons of record, the rejection stands.

The rejection of claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 31-32 above, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757, is maintained.

Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments are based on their previous argument that Hurpin in view of Hodge, Rice, and Lehner do not provide a reasonable expectation of success to arrive at the instant invention as claimed. These arguments have been fully considered and addressed in detail above and have not been found persuasive. Applicant's further argument that Zaremba et al. and Salgaller et al. do not overcome the deficiencies of Hurpin, Hodge, Rice, and Lehner is not persuasive as the teachings of Hurpin, Hodge, Rice, and Lehner stand, as discussed above, and Zaremba and Salgaller were not cited to teach lymph node administration, rather these references were cited to provide teachings and motivation to immunize with tumor antigens which comprise the sequence YLSGADLNL or YLEPGPVTV. The applicant has not traversed these teachings, therefore, the rejection of record stands.

The rejection of claims 21-27 and 31 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 31-32 above, and further in view of Barnett et al. (1997) Vaccine, Vol. 15(8), 869-873, is withdrawn over canceled claim 31 and maintained over previously pending claims 21-27. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments are based on their previous argument that Hurpin in view of Hodge, Rice, and Lehner do not provide a reasonable expectation of success to arrive at the instant invention as claimed. These arguments have been fully considered and addressed in detail above and have not been found persuasive. Applicant's further argument that Barnett does not overcome the deficiencies of Hurpin, Hodge, Rice, and Lehner is not persuasive as the teachings of Hurpin, Hodge, Rice, and Lehner stand and Barnett was not cited to teach lymph node administration, rather Barnett was cited to provide teachings and motivation to immunize using a prime/boost vaccination strategy which includes a priming step with a nucleic acid encoding an antigen and a boosting step with a protein form of the antigen. The applicant has not traversed these teachings, therefore, the rejection of record stands.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the new technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633